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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,943	POULOSE ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship to priority under 35 U.S.C. § 119 of the 16 January 2002 filing date of the parent US provisional application serial No. 60/350,221, and its successor International patent application PCT/US03/01447 filed 16 January 2003, of which the instant application is a National Stage filing under 35 U.S.C. § 371, is hereby acknowledged.

Information Disclosure Statement

No Information Disclosure Statement [IDS] has yet been filed in this application.

Election and Preliminary Amendment

Applicant's election without traverse in the Response filed 23 December 2005 of the invention of Group III, subtilisin variants comprising a first amino acid substitution at the subtilisin BPN'-correspondent position 170, wherein a species of secondary substitution of Group E at position 87 is further elected, is acknowledged. Applicant's Preliminary Amendment filed on 23 December 2005, has been entered. While Applicant indicates that claims 4 and 6 are withdrawn from consideration, both claims include the elected variant of Group III, thus claims 1-10 remaining in the application are examined herein.

Objections to the Specification

The specification is objected to for reciting, at page 1, the undefined term "carbonyl hydrolases" because it fails to indicate any particular group of polypeptides or enzymes that have a structure within which a structure of a serine protease might be recognized.

The specification is further objected to for omission of the provisional application serial No. 60/440,792 at line 12 of page 18.

Compliance with 37 CFR § 1.821 is required in response to this Office action. Page 2, line 23, lacks a designation describing the recited amino acid positions according to

requirements of 37 CFR § 1.821 for a Sequence Disclosure which call for a statement in the form of the designation "**SEQ ID NO:n**", where "n" is an integer corresponding to the Sequence Disclosure, whether a sequence is referred to in whole or in part. At page 2, the several positions are indicated without reference to a particular sequence, where the amino acid sequence of SEQ ID NO:2 is intended. (2) In addition, page 37 lacks the necessary designations, at lines 7 and 10, for the nucleotide sequences of the disclosed forward and reverse primers. (3) While Applicant's PCT priority document provides a Sequence Listing, there is no printed sequence listing present in the file of the instant application. Each of these three defects must be corrected in response to this communication and a Statement of Sameness of the printed and computer-readable forms of the sequence listing must also be submitted. Please also note that if the nucleotide sequences of the primers disclosed at page 21 were **not** provided in the computer readable form [CRF] of the sequence listing submitted in the priority document, or if Applicant desires that the amino acid sequence of GG36 subtilisin be disclosed in the specification, such further oligonucleotide and amino acid sequences **MUST** be included in both (a) a revised/amended printed form of the sequence listing and (b) a revised computer readable form [CRF] that must both be submitted in response to this communication, again with an accompanying Statement of Sameness. See 37 CFR §§ 1.821(b), (c) and (d).

Claim Objections

Claims 3-5 are objected to for the following informalities:

Claim 3 is objected to because it mistakenly recites, "at one or more residue positions equivalent to residue positions selected from the group consisting of", yet the claim amendment results in the recitation of a single position in the claim. Appropriate correction is required, e.g., amending claim 3 to recite "having a substitution at the a

position corresponding to position 70 in the subtilisin amino acid sequence set forth in SEQ ID NO:2."

Claim 4 is objected to because it mistakenly recites, "comprises comprising". Appropriate correction is required, e.g., amending claim 4 to recite "wherein the variant comprises the substitution R170S".

Claim 5 is objected to because it fails to provide number agreement in reciting "**an** additional substitution at **positions** corresponding to position 87", where only a single position is indicated. Appropriate correction is required, e.g., amending claim 5 to recite "further comprising an additional substitution at the position corresponding to position 87 in the subtilisin amino acid sequence set forth in SEQ ID NO:2."

Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place it in proper dependent form, or rewrite the claim in independent form. Claim 6 fails to limit claim 5 by providing a pair of specific substitutions at the two positions required by claims 3 and 5 and is advantageously either restated as an independent claim or amended to depend from claim 3 or claim 4.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 7-10 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of generic divergent proteases of claims 1 and 2, which may be taken from any class of proteases and may

differ to any extent from a native protease by any number of amino acid "modifications" that may be, at the least, substitutions, additions, or deletions of amino acids, or the preparation of polynucleotides encoding such generic divergent proteases. Neither the claims nor the specification describe the nature of proteases wherein such "modifications" might occur, nor what the nature of any "modifications" might be, except for members of the class of secreted, monodomain, serine proteases recognized in the art as subtilisins or subtilases. The specification does not otherwise disclose or suggest the nature or source of any serine proteases that might be modified according to the disclosure of the specification. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any undisclosed classes of serine proteases to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of serine proteases that might be modified according to recitations of claims 1 and 2.

Claims 1, 2 and 7-10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the modification of members of the class of serine proteases known as subtilisins, or subtilases, where positions for modification can be identified by correspondence with positions in the amino acid sequence set forth in SEQ ID NO:2, does not reasonably provide enablement for modification of members of other classes serine proteases or proteases generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 2 contemplate arbitrary modification of members of any class of proteases, or any class of serine proteases, by introducing any number of amino acid substitutions, additions or deletions anywhere in the amino acid sequence of a generic precursor protease and the preparation of polynucleotides encoding generic divergent proteases. Yet the specification cannot support the introduction of any number amino acid sequence alterations in the amino acid sequences of proteases generally, in any combination or any pattern, and even taken together with the prior art made of record herewith cannot identify amino acid positions in sequences of generic proteases that might be altered, nor teach the nature of the alterations to be made, without establishing correspondence with the positions in the subtilisin BPN' sequence set forth in SEQ ID NO:2. It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection for non-enablement under 35 U.S.C. §112, first paragraph. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering even serine protease amino acid sequences structurally unrelated to the amino acid sequence set forth in SEQ ID NO:2,

b) the specification lacks working examples wherein protease amino acid sequences unrelated to the sequence set forth in SEQ ID NO:2, are altered,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of other classes of serine proteases having amino acid sequences unrelated the amino acid sequence of the mature subtilisin BPN' set forth in SEQ ID NO:2 have had more than a few amino acids identified for concurrent modification.

The scope of the divergent proteases embraced by claims 1 and 2, and their encoding polynucleotides of claims 7-10, is unsupported by the specification and the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it describes a protease variant as "comprising one or more modifications at a . . . residue position", yet "having the same net electrostatic charge", which ambiguously indicates that several modification may be made at any particular, charged position so that sum of modifications made at one position result in no change in net electrostatic charge. The specification does not teach how this might be accomplished and instead teaches preparing modifications at more than one position where the several modifications produce no change in the net electrostatic charge of a protease variant, thus claim 1 fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2-10 are included in the rejection of claim 1 because they fail to remedy its indefinite description.

While claim 4 is not improperly dependent insofar as claim 3 from which it depends currently recites "comprises", and claim 4 may further comprise a substitution at another position, claim 4 is rejected as indefinite because it describes a variant of claim 3 wherein "a substitution . . . is a substitution", failing to clearly indicate that **the** substitution in the variant of claim 3 is combined with another substitution. When claim 3 is amended to overcome the objection to the claim stated at page 3 above, claim 4 may advantageously be amended to overcome this rejection by stating only the disclosed R170S substitution.

Claim 6 is indefinite in reciting "[t]he . . . variant of claim 5 wherein the variants are selected from the combinations of" because no preceding claim provides a basis for the several combinations that combine amino acid substitutions at positions beyond the

subtilisin BPN'-correspondent position 170 with a substitution at position 170. This aspect of the rejection may be overcome by amending claim 6 to state, "[t]he . . . variant of claim 3 comprising a pair of substitutions selected from the pairs of substitutions consisting of A1R+R170S, G61R+R170S, G101R+R170S, R170S+N204R, and R170S+S216R."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3 and 7-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by the disclosure of Vetter et al., US 5,453,372, of preparation of subtilisin variants having a substitution of an uncharged amino acid for arginine at position 164 in their *Bacillus alcalophilus* subtilisin, a position corresponding to the subtilisin BPN' position 170, that may be further combined, see claim 1, with a substitution of a positively-charged amino acid for an uncharged amino acid at another position, e.g., I43K or I43R, corresponding to the subtilisin BPN' position 44, or T249K or T249R, corresponding to the subtilisin BPN' position 255, resulting in a subtilisin variant meeting structural limitations of claims 1-3 and having the same net electrostatic charge as the precursor subtilisin protease. Vetter et al. also disclose the subject matters of pending claims 7-10 in Figures 1-8, particularly Figure 3B, and at columns 7-26.

Claims 1-4 and 7-10 are rejected under 35 U.S.C. § 102(e) as being anticipated by the disclosure of van der Osten et al., US 6,300,116, made of record herewith, of

preparation of subtilisin variants wherein an uncharged amino acid, such as serine, is substituted for arginine at a position corresponding to the subtilisin BPN' position 170 in any subtilisin, R170S, that is further combined, see col. 19 at lines 3 and 14, with a substitution of a positively-charged amino acid for an uncharged amino acid, either P129K or F189K, resulting in a subtilisin variant meeting structural limitations of claims 1-4 and having the same net electrostatic charge as the precursor subtilisin protease. Van der Osten et al. also disclose the subject matters of pending claims 7-10 at columns 19-46.

Claims 1-5 and 7-10 are rejected under 35 U.S.C. § 102(e) as being anticipated by the disclosure of Hansen et al., US 6,605,458, made of record herewith, of preparation of subtilisin variants having serine substituted for arginine at a position corresponding to the subtilisin BPN' position 170 in any subtilisin, R170S, that is further combined, see claims 17-22, 39-44, 66-71, and particularly claims 22, 44 and 71, with a substitution of a positively-charged amino acid for an uncharged amino acid, P129K, resulting in a subtilisin variant meeting structural limitations of claims 1-4 and having the same net electrostatic charge as the precursor subtilisin protease. Hansen et al. are further considered to disclose the subject matter of claim 5 herein by also permitting the substitution S87N in claims 19, 41 and 68. Hansen et al. further disclose the subject matters of the pending claims 7-10 in claims 23-27, 45-50 and 72-76.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Because claim 6 describes no substitution at the position required by claim 5, it is examined as though it instead referred back to either claim 3 or claim 4. Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over either of van der Osten et al., or Hansen et al., as applied to claims 1-4 above, in view of Vetter et al., US 5,352,603, made of record herewith. The teachings of van der Osten et al. and Hansen et al., discussed above, are taken as before. Vetter et al., US 5,352,603 teach, see claim 1, the substitution of the amino acid, which is the uncharged asparagine, at position 198 in the in their *Bacillus alcalophilus* subtilisin, a position corresponding to the subtilisin BPN' position 204, with either arginine or lysine, because such substitutions confer optimal proteolytic activity in an alkaline pH range. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine a R170S substitution of either of van der Osten et al., or Hansen et al. with a N204R substitution of Vetter et al., '603, as a substitution for the P129K substitution of Hansen et al. or the P129K or F189K of van der Osten et al. This is because such an artisan at that time would have been motivated to do so because s/he would have appreciated that the N204R substitution of Vetter et al., '603, would advantageously balance a R170S substitution of van der Osten et al. and Hansen et al. in order to maintain an optimal proteolytic activity in an alkaline pH range, a pH range encountered in most detergent compositions as admitted by the instant application and well-known to such an artisan at that time as exemplified by the teachings of the prior art of record. Such an artisan would have had a reasonable expectation of success in so doing because the highly alkaline *Bacillus alcalophilus* subtilisin is structurally closely related to the highly alkaline subtilisin PB92 and subtilisin 309 proteases of van der Osten et al. and Hansen et al.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
13 March 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER